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TUMORS IN DOGS.

JONATHAN FORMAN AND CARLOS I. REED.

I. Carcinomas of the Thyroid Gland.

This paper embraces the anatomical description of fifteen enlargements of the thyroid glands of dogs and an attempt to correlate these with well known types of thyroid carcinoma in the human as well as with the general principles of oncology.

The frequent occurrence of tumors among vertebrates is well recognized. Numerous workers have reported the occurrence of malignant new-growths in both wild and domestic animals. Cancer has been found more frequently among the domesticated animals. The incidence curve of malignancy in dogs approaches that of the human.

In his discussion of the frequency of cancer in dogs, Wolff ('13) cites one series of dogs reported from the Berlin veterinary clinic in which 1.9% of all sick dogs exhibited some form of malignancy. In another series, the incidence was 3%, while in a third series there was an incidence of 5.5%; a fourth series showed an incidence of 7% and a fifth series showed a malignancy incidence of 8%. From these data it was also shown that the greatest incidence of cancer among dogs occurs at about the eighth year of life. Goodpasture and Wislocki ('16),

who have made a study of fifteen old dogs, report a remarkable series of multiple tumors. There were fourteen cases each of tumor of the liver, spleen, and adrenals; eight cases each of tumor of the gall-bladder and prostate; five cases each of tumor of the stomach and ovary; four of the subcutaneous tissues; two cases each of the submaxillary gland, testes, and breast; one case each of the following: pancreas, parotid, thymus, skin, hypophysis, blood vessels and bladder. In only one of these cases, that of a malignant tumor arising from the medulla of the right adrenal, was there any metastatic manifestation found and in this case there were metastatic nodules in the liver. All the other tumors were primary. In five dogs of this series there were also multiple carcinomas of the thyroid gland which were primary. In three cases, both lobes were involved.

Several other workers have reported cases of primary carcinoma of the thyroid gland of dogs. Sarcomas are very rare. Wells ('01) and Schoene ('09) have each reported a case occurring in a dog in which the thyroid tumor was composed of connective tissue and epithelium—the so-called sarco-carcinomas.

During the school year of 1915-16 a systematic search was made for tumors occurring in the dogs used in the Laboratories of Physiology and Pharmacology. Especial attention was given to the thyroid gland. Every gland was routinely sectioned and microscopical preparations were made. There are 234 glands in this series. During the first four months of the present school year (1916-17), 37 additional thyroid glands have been routinely examined in the same way, making a total of 271 cases in the complete series. In these 271 thyroid glands, five malignant tumors were encountered. This gives an incidence of 1.8%. During the two previous years, such tumors as attracted attention in these Laboratories were sent to the Pathological Laboratory for examination. Five cancers of the thyroid were observed in this way. At various times specimens of tumors occurring in dogs have been presented to the laboratory. In this series are five cancers of the thyroid gland. No sarcomas of the thyroid were encountered. This study is, therefore, based upon fifteen specimens of carcinoma of the thyroid of dogs. Since the specimens fall into four distinct groups, individual protocols have been omitted and those cases resembling each other closely have been described as a group.

GROUP 1. Two tumors fall into this group. Each presents a fairly definitely encapsulated nodule in a gland, both of whose lobes are enlarged to about an equal extent. The one was from an old male and the other from a rather old female in a late stage of pregnancy. In the gross, each nodule is buried in the substance of the gland, but its outline can be distinctly made out on the surface before sectioning. Each nodule is surrounded by dense fibrous tissue and composed of a soft and apparently very cellular tissue.

Microscopical examination reveals compressed, but fairly normal thyroid tubules surrounding the nodule. The cells of these tubules are cuboidal. The lumina are irregularly ovoid in shape due to compression. The secretion is small in amount and only faintly stained with eosin. Within a capsule of dense connective tissue can be seen a mass of epithelial cells resting in scant stroma. (Fig. 1). There are, however, a few trabeculae running through the tumor and these have taken on a mucoid appearance, a change which is frequently seen in the connective tissue supporting the tumors of the thyroid. Among the tumor cells, every stage of transition can be seen from solid cords of cells to tubules containing colloid and resembling closely those of the normal gland. Mitotic figures are difficult to find. On account of the greater lack of differentiation on the part of the epithelium, the more extensive necrosis and the more definite invasion of the capsule, the distinct impression is gained that the second tumor is growing much more rapidly than the first. It is of especial interest since pregnancy usually exerts an inhibitory influence of neoplastic activity. In both specimens the point of invasion of the capsule is adjacent to the cells, showing the greatest lack of differentiation. As was noted in the second specimen a goodly portion of the center of the nodule has undergone necrosis. At the margin of this necrotic area, the cells have arranged themselves concentrically around blood vessels. The intervening tissue is necrotic, so that a peritheliomatous appearance is given to the tumor at these points. In the second specimen, also, tumor cells are observed growing in the lymph spaces. No metastasis is demonstrable in either instance.

The enlargement in these glands is due to a definite cancer not unlike the so-called proliferating struma seen in the thyroid gland of man. Apparently, also, here as in man, the tumor

does not belong to the more malignant variety. The presence of a growth in the lymph spaces suggests, however, that metastasis would have occurred at no distant date had the animal been allowed to live.

GROUP 2. Into a distinct group fall two other cases. Both of these tumors occurred in old males. The gland is extensively involved by the new-growth. Some seven or eight nodules are found in a single lobe. These vary in size from 5 to 20 mm. in diameter. The centers of the nodules in some instances are necrotic. The tumor substance itself is yellowish white. A striking coloring is lent to the gross sectional appearance of the specimen by the necrosis and by the presence of hemorrhage both into the tumor mass and into the gland substance.

Bands of connective tissue separate the masses of tumor cells, giving an alveolar arrangement to the tumor. The stroma in both cases has taken on a mucoid appearance and presents many slit-like cavities from which crystals have been dissolved. There is little in these neoplasms as seen microscopically to remind one of the thyroid gland. In the one specimen, a few tubules which are normal in appearance can be seen (Fig. 2), but the arrangement of the tumor cells in and around these reefs of thyroid tubules makes it seem more probable that these are remnants of the normal gland structure than that the tumor cells should have differentiated in such an oddly shaped zone. In certain areas, the typical tumor cells are small and round with deeply staining nuclei (Fig. 3). In certain other areas, however, the tumor cells have assumed a spindle shape and this makes it difficult to distinguish this tumor from a sarcoma composed of small round and spindle-shaped cells. It would, indeed, be very easy, upon casual examination to mistake the growth for the so-called sarco-carcinoma. One must be careful to distinguish these growths from those tumors of the thyroid in which both the connective tissue and epithelial elements have taken on a neoplastic character. The progression from the areas of an undoubted carcinomatous nature to areas of a sarcomatoid character can be followed without interruption. A study of the pulmonary metastasis which has occurred in one of these cases reveals a typical carcinomatous secondary growth. These facts, it seems, warrant the diagnosis of carcinoma.

Fig. 4 is introduced from a spindle cell carcinoma occurring in the thyroid gland of a horse. The elongated epithelial tumor cells may be seen arranged in a kind of bundle formation so that the resemblance to neoplastic connective tissue cells (a sarcoma) is even more striking than in the canine specimens. Areas can be found in which the carcinomatous cells appear to be distinct from the sarcomatoid groups. If these strands of spindle cells are followed, it is observed that the cells change to spherical shape and then are arranged into more or less definite tubules. So that, while these specimens, upon casual examination appear to be adeno-sarcomas or sarco-carcinomas, a more careful study makes it appear that there is only one type of tumor cells present and that these are epithelial cells. This is in agreement with the observation of Ewing ('16) that "epithelial tumors may from their inception appear like spindle cell sarcomas as, in the spindle cell carcinoma of the thyroid. It is becoming more and more apparent that many so-called sarcomas of the organs are in reality spindle cell carcinomas."

A more decided lack of differentiation of the tumor cells in both specimens and the presence of metastasis in the one instance indicate that this is a more malignant type of cancer as compared to those in Group 1.

GROUP 3. Ten specimens are placed in this group which appear much the same as carcinoma seen in other organs and as seen most frequently in the thyroid gland of man. A whole lobe and often both lobes are involved in the growth. The tumor substance is of a pearly white color except where it has undergone necrosis or a hemorrhage has occurred into it. The tumor is subdivided into smaller spheroid masses, measuring 1 to 5 cm. in diameter, by strands of fibrous tissue. The gross sectional appearance and the extent of the involvement can be seen in Fig. 9.

The tumor cells vary in size, shape and arrangement. Six of these specimens show a tendency to form tubules. The cells are cuboidal for the most part. In certain tubules, however, they are high columnar. An occasional tubule is well formed and contains colloid.

All stages of transition from the more nearly normal tubules to strands of typical tumor cells, and further still, to masses of cells with no definite arrangement, supported in a delicate

stroma. These masses may be separated by bands of dense connective tissue and thus given an alveolar arrangement. It is in these masses, that the greatest variation is seen, both in the same tumor and in different tumors. In seven of the specimens, the cuboidal cell is the predominating one. Occasionally a mass of large spherical cells with clear, lightly staining cell bodies and small dark nuclei are encountered. In three of the specimens, this same type of cell predominates so that these specimens appear to be of the medullary type of carcinoma. In many instances the blood vessels are filled with the growth.

In six of the cases, definite metastatic nodules are present in the lungs (Fig. 10). Unfortunately, a search through the marrow of the bones of each animal could not be made. Since this is a frequent site for the secondary growth of thyroid tumors, no doubt, instances of metastasis might have been found. In the lungs presenting metastatic nodules, many of the vessels are filled with tumor cells. One of these specimens illustrates defense against the tumor cell which has found its way into the circulatory system. That is, there is a proliferation of endothelium and an ingrowth of connective tissue in and around the embolic mass of tumor cells to such an extent that the tumor cells have been completely crowded out. (Figs. 5, 6, 7, 8). These tumors are distinctly malignant. The number of metastases indicates this as well as the histological picture.

GROUP 4. Another form of thyroid malignancy is illustrated by a single specimen in our series. The greater part of this tumor was not brought to the laboratory, but was used by Drs. Scott and Dodd in an unsuccessful experiment in transplantation. Our description of the specimen, therefore, rests on the findings in four blocks of tissue embedded in celloidin. The growth is composed of whitish nodules and cystic cavities filled with the tumor growth.

Microscopical examination reveals dilated gland lumina into which extend many papillary growths of connective tissue covered with epithelial cells of columnar type. (Fig. 17). The tendency to develop into a papilliferous growth is seen even in the more solid nodules of the tumor. The papillary cystadenoma is encountered occasionally in the human and is usually placed in a class between benign and malignant growths.

Two of the four specimens studied by Muller and Speese ('06), had undergone carcinomatous change. The character of these solid nodules is definitely carcinomatous. This specimen is, therefore, to be classed as a cystocarcinoma papilliferum.

SUMMARY.

These enlargements of the thyroid gland are all due to a new growth of the glandular epithelium. The cells of this new growth do not present the differentiation typical of thyroid epithelium. They have lost for the most part their polarity and normal arrangement. In certain instances these losses are so marked that from individual sections it could not be ascertained that the tissue was at all related to the thyroid gland. All gradations between this and definite tubules containing colloid are observed. The growths are not localized but have infiltrated more or less the surrounding glandular structure. In the more advanced cases, secondary nodules are found in distant parts, particularly in the lungs. Since infiltration and metastasis are late manifestations of most carcinomas, it is not surprising to find that several of these tumors taken from dogs which were apparently healthy should present secondary nodules and that the infiltration seen in the specimens presenting only single small nodule should not be as yet extensive.

The incidence of malignancy in our series is somewhat higher than in the human. In 5,000 goitre patients treated at the Mayo Clinic, ('13), 52 carcinomas were found. It is to be noted that this series of dogs, not selected but taken as they came into the laboratory, and therefore, representing the average healthy dogs of Columbus, present a malignancy incidence nearly equal to that of the Mayo series of humans selected because of diseased thyroid glands. In Ohio (1910-1913), the mortality from goitre was 21.2 per 100,000 persons living. Many of these were non-malignant diseases of the gland since all fatal diseases of the thyroid are returned as goitre.

Because of the source of the material, the exact ages of the dogs could not be determined except in one instance in which by accident the dog was known to be twelve years old. All the others, however, appeared to be old dogs as judged by the general appearance and activity of the animals and the condition of their teeth.

These groups of carcinoma are similar to those already described for thyroid carcinoma in man. This is in agreement with the findings of others concerning the wide zoological distribution of cancer and serves to emphasize the fact that the cancer problem has a wide biologic connection.

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